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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/460,186	06/02/1995	REID VON BORSTEL	1331-138	5103

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EXAMINER	
OLSON, ERIC	
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1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/460,186	VON BORSTEL ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

In view of the appeal brief filed on December 21, 2007, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623

This application is a divisional application of US application 08/176485, now US patent 5736531, filed December 30, 1993, which is a continuation in part of US application 08/061381, now abandoned, filed May 15, 1993, which is a continuation in part of US application 07/903107, filed June 25, 1992, now abandoned, which is a continuation in part of US application 07/724340, now abandoned, filed July 5, 1991,

which is a continuation in part of US applications 07/438493, now abandoned, filed June 26, 1990, and 07, 487984, now abandoned, filed February 5, 1990, both of which are continuations in part of US application 07/115923, now abandoned, filed October 28, 1987.

Claims 1-25 are pending in this application.

Claims 1-25 as amended are examined on the merits herein.

Applicant's arguments, submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under 35 USC 112, first paragraph for lacking enablement for all acylated non-methylated pyrimidine nucleosides, has been fully considered and found to be persuasive to remove the rejection because the claimed compounds are a structurally limited class of compounds that could reasonably be obtained and evaluated by one skilled in the art in order to practice the claimed invention undertaking only routine, predictable experimentation. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 5246708, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 5470838, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 5583117, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 5691320, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6020320, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6020322, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6060459, have been fully considered and found to be persuasive to remove the rejection as this application claims a method

comprising administering acylated purines, rather than pyrimidines. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6232298, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6255290, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6274563, have been fully considered and

found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6316426, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6403565, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

Applicant's arguments submitted December 21, 2007, with respect to the rejection of instant claims 1-25 under the doctrine of obviousness-type double patenting for claiming the same invention as US patent 6417170, have been fully considered and found to be persuasive to remove the rejection as this application does not claim a method wherein the subject would be considered to be suffering from or at risk of developing toxicity due to a pyrimidine nucleoside analog. Therefore the rejection is withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are directed toward a method comprising administering an acylated **derivative** of a pyrimidine nucleoside, and of treating toxicity due to a pyrimidine nucleoside **analog**. It is not clear what is meant by an analog or derivative. One skilled in the art would consider the terms "derivative" and "analog" as referring to compounds bearing some sort of structural similarity to pyrimidine nucleosides. However, one skilled in the art would not be able to clearly and distinctly determine what compounds bear sufficient similarity to be considered to be

derivatives or analogs. In the absence of any way of clearly and distinctly defining the boundaries of this class of compounds, these claims are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating, reducing, or ameliorating the toxicity of a pyrimidine analog, does not reasonably provide enablement for preventing said toxicity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of toxicity from one therapeutic agent by administering a second therapeutic agent. In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. Merriam-Webster's Collegiate Dictionary (reference included with PTO-892) defines "prevent" as meaning, "to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "preventative". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prevention" as recited in the instant claims, is interpreted to mean the complete and

total blocking of all symptoms of a disorder for an indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The state of the prior art: Certain nucleoside derivatives are known in the art to be useful for treating cancer or viral infections. These classes of compounds are also known to be toxic to normal non-malignant, uninfected cells. It is known that this toxicity can be reduced in certain instances by administration of pyrimidine nucleosides. However, this treatment does not qualify as a preventative treatment in the sense described above under the heading "Nature of the invention"

More generally, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder.

The amount of direction or guidance presented: The claimed acylated pyrimidines are shown to be capable of reversing the toxicity of certain nucleosides such as AZT and Tegafur. However, no guidance is given in the specification suggesting any reason to believe that administration of an acylated non-methylated pyrimidine can fully prevent the later occurrence of toxicity arising from administration of a pyrimidine nucleoside analog.

The presence or absence of working examples: While various working examples are provided of the protection of living subjects from nucleoside-induced toxicity by concurrent administration of acylated pyrimidines, these working examples do not show prevention, in the broadest interpretation as described under the heading, "Nature of the Invention."

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the nature of the invention and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of toxicity.

Claims 18, 20, 22, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods involving certain specific uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, and enhancers of uptake and phosphorylation of nucleosides, such as those recited in instant claims 19, 21, and 23, does not reasonably provide enablement for methods involving administering all possible compounds of these types. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed method is a therapeutic method comprising administering several active agents. In order to be enabled to practice a therapeutic method, one skilled in the art must be able to readily determine which compounds are useful in the claimed method and to obtain said compounds.

The state of the prior art: It is well known in the prior art that certain compounds are uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, and enhancers of uptake and phosphorylation of nucleosides. However, the prior art does not reveal the full scope of all possible compounds having these activities, or provide any formula or other means by which one skilled in the art could determine the full scope of which compounds are reasonably considered to have any of the recited activities.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Although compounds having a similar structure are usually expected to possess similar biological activity, it does not therefore follow that one can predict all of the biological activities of a particular novel compound merely by contemplating the structure. Rather, in order to determine the full scope of a particular class of compounds (e.g. uridine phosphorylase inhibitors) one skilled in the art would have to obtain and test a wide range of unrelated compounds for the desired activities.

Still further, there exist many potential compounds that are difficult to obtain. Not all compounds that could be conceivably evaluated as therapeutic agents can be obtained commercially or synthesized without unpredictable experimentation. Rather, some of these compounds would require a difficult process of unpredictable experimentation in order to develop a novel synthesis whereby they could be manufactured. This process would have to be repeated many times in order to obtain a

set of compounds that is fully representative of the full range of available chemical diversity.

The Breadth of the claims: The claimed invention is very broad, encompassing methods of administering a pyrimidine nucleoside and an acylated non-methylated pyrimidine in which in which any additional compound that happens to be a uridine phosphorylase inhibitor, cytidine deaminase inhibitor, nucleoside transport inhibitor, enhancer of hematopoiesis, or enhancer of uptake and phosphorylation of nucleosides

The amount of direction or guidance presented: Applicant's specification discloses that uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, and enhancers of uptake and phosphorylation of nucleosides can enhance the activity of, or reduce the toxicity of, pyrimidine nucleoside analogs. The specification does not provide any guidance for the discovery and testing of novel compounds of these classes that are not already known in the art.

The presence or absence of working examples: While the specification provides working examples demonstrating the utility of certain acylated pyrimidines for reversing the toxicity from nucleoside analog chemotherapeutic and antiviral agents, no working examples are provided demonstrating the utility of any particular uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, or enhancers of uptake and phosphorylation of nucleosides for this purpose.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, and enhancers of uptake and phosphorylation of nucleosides beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful in one of these roles. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have one of the desired activities. For most compounds, it is unknown whether they are or are not useful as uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors, enhancers of hematopoiesis, or enhancers of uptake and phosphorylation of nucleosides. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for the recited activities, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable

synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential compounds, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible potential therapeutic agent, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of compounds claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all possible uridine phosphorylase inhibitors, cytidine deaminase inhibitors, nucleoside transport inhibitors,

enhancers of hematopoiesis, and enhancers of uptake and phosphorylation of nucleosides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaguchi et al. '139 (US patent 4757139, cited in PTO-892) or the equivalent to PCT publication WO85/00608, published Feb. 14, 1985) Kawaguchi et al. '139 discloses an acylated pyrimidine nucleoside analog, specifically an acylated 5-fluoro-2'-deoxyuridine. (column 2 lines 15-38) This compound shows strong antitumor activity even in low doses and has a markedly improved therapeutic index over the parent compound 5-fluoro-2'-deoxyuridine. (column 2 lines 39-48) The acylated compounds show sustained release of 5-fluoro-2'-deoxyuridine and prolong the survival of tumor-bearing mice. (column 3 lines 47-66) Kawaguchi et al. '139 does not disclose a method whereby these acylated compounds are substituted for 5-fluoro-2'-deoxyuridine in order to prevent or treat toxicity due to this compound.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prevent or treat toxicity due to 5-fluoro-2'-deoxyuridine by administering the controlled release esters of Kawaguchi et al. '139 instead of unmodified 5-fluoro-2'-

deoxyuridine. One of ordinary skill in the art would have been motivated to use the compound in this manner because Kawaguchi et al. '139 already discloses that the esters of 5-fluoro-2'-deoxyuridine are useful for treating cancer and have a better therapeutic index than the parent compound, providing the expectation that they will be safer and produce fewer side effects. One of ordinary skill in the art would reasonably expect success because using delayed-release pharmaceutical agents to reduce the side effects of a therapy is well known and routine in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1-5, 8, 10, 11, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai et al. (Foreign Patent JP-S60-126221, reference included with PTO-892) Takai et al. discloses an antitumor composition comprising 5-fluoro-2'-deoxyuridine (I) and a thymidine compound that can be an acylated thymidine. (abstract, also p. 140) When this composition is administered to a subject the antitumor activity is preserved while the toxicity and side effects are mitigated. (abstract) Therefore Takai et al. describes a method of treating toxicity due to a pyrimidine nucleoside analog by administering an acylated derivative of a pyrimidine nucleoside. Takai et al. does not disclose a method whereby the acylated pyrimidine nucleoside is non-methylated (i.e. uridine).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute acylated uridine for acylated thymidine in the methods of Takai et al. One of ordinary skill in the art would have been motivated to make the substitution

because the two compounds differ by only a single methyl group. It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. See *In re* Lincoln, 126 USPQ 477, 53 USPQ 40 (CCPA 1942); *In re* Druey, 319 F.2d 237, 138 USPQ 39 (CCPA 1963); *In re* Lohr, 317 F.2d 388, 137 USPQ 548 (CCPA); *In re* Hoehsema, 399 F.2d 269, 158 USPQ 598 (CCPA 1968); *In re* Wood, USPQ 148 (CCPA 1977); *Ex parte* Fauque, 121 USPQ 425 (POBA 1954); *Ex parte* Henkel, 130 USPQ 474, (POBA 1960)

Thus the invention taken as a whole is *prima facie* obvious.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaguchi et al. (US patent 4757139, cited in PTO-892) or the equivalent to PCT publication WO85/00608, published Feb. 14, 1985) as applied to claims 1-5, 8, 10, and 11 above and further in view of Chu et al. (Reference included with PTO-892) The disclosure of Kawaguchi et al. is discussed above. Kawaguchi et al. does not disclose a method additionally including administering an inhibitor of uridine phosphorylase.

Chu et al. discloses the enhancement of the neoplastic activity of 5-fluoro-2'-deoxyuridine by benzylacyclouridine and benzyloxybenzylacyclouridine, both of which are inhibitors of uridine phosphorylase. (p. 1852, right column, second paragraph, p. 1854, right column paragraph 2 and table 3)

It would have been obvious to one of ordinary skill in the art at the time of the invention to additionally administer benzylacyclouridine or benzyloxybenzylacyclouridine in the method of Kawaguchi et al. One of ordinary skill in the art would have been

motivated to administer this compound because Chu et al. already discloses that it is useful for increasing the antitumor effect of 5-fluoro-2'-deoxyuridine. One of ordinary skill in the art would reasonably have expected success in doing so because Chu et al. already demonstrates the improved efficacy of the combination of 5-fluoro-2'-deoxyuridine with benzylacyclouridine *in vivo*. Note that although the compound administered in the method of Kawaguchi et al. is not 5-fluoro-2'-deoxyuridine as such, it is a prodrug of 5-fluoro-2'-deoxyuridine, and is expected to lead to therapeutic 5-fluoro-2'-deoxyuridine levels in the subject.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai et al. (Foreign Patent JP-S60-126221, reference included with PTO-892) as applied to claims 1-5, 8, 10, 11, and 17 above and further in view of Chu et al. (Reference included with PTO-892) The disclosure of Takai et al. is discussed above. Takai et al. does not disclose a method additionally including administering an inhibitor of uridine phosphorylase.

Chu et al. discloses the enhancement of the neoplastic activity of 5-fluoro-2'-deoxyuridine by benzylacyclouridine and benzyloxybenzylacyclouridine, both of which are inhibitors of uridine phosphorylase. (p. 1852, right column, second paragraph, p. 1854, right column paragraph 2 and table 3)

It would have been obvious to one of ordinary skill in the art at the time of the invention to additionally administer benzylacyclouridine or benzyloxybenzylacyclouridine

in the method of Takai et al. One of ordinary skill in the art would have been motivated to administer this compound because Chu et al. already discloses that it is useful for increasing the antitumor effect of 5-fluoro-2'-deoxyuridine. One of ordinary skill in the art would reasonably have expected success in doing so because Chu et al. already demonstrates the improved efficacy of the combination of 5-fluoro-2'-deoxyuridine with benzylacyclouridine *in vivo*.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-6, 8, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaguchi et al. '162 (US patent 4868162, cited in PTO-892) Kawaguchi et al. discloses an acylated pyrimidine nucleoside analog, specifically an acylated 5-halo-2'-deoxyuridine, such as fluoro-, chloro-, or bromo- nucleosides, which are antiviral agents. (column 2 lines 1-23) This compound shows strong antiviral activity even in low doses and has a markedly improved therapeutic index over the parent 5-halo-2'-deoxyuridines. (column 2 line 56 – column 3 line 18) Kawaguchi et al. '162 does not disclose a method whereby these acylated compounds are substituted for 5-fluoro-2'-deoxyuridine in order to prevent or treat toxicity due to this compound.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prevent or treat toxicity due to 5-fluoro-2'-deoxyuridine by administering the controlled release esters of Kawaguchi et al. '162 instead of unmodified 5-halo-2'-deoxyuridines. One of ordinary skill in the art would have been motivated to use the compound in this manner because Kawaguchi et al. '162 already discloses that the

esters of 5-halo-2'-deoxyuridine are useful for treating viral infections and have a better therapeutic index than the parent compounds, providing the expectation that they will be safer and produce fewer side effects. One of ordinary skill in the art would reasonably expect success because using prodrugs of pharmaceutical agents to reduce the side effects of a therapy is well known and routine in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 and 14-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5968914. (Cited in PTO-892, herein referred to as '914) Although the conflicting claims

are not identical, they are not patentably distinct from each other because claims 1-23 of '914 anticipate the claimed invention. Specifically, claim 1 of '914 is drawn to a method for treating cancer comprising administering a high dose of a pyrimidine nucleoside analog in combination with an acyl derivative of a non-methylated pyrimidine nucleoside. This is the same combination of active agents claimed in the instant claims and would inherently lead to the same toxicity-reducing effect. Claims 2-5, 14, and 15 of '914 recite specific pyrimidine nucleoside analogs used in the instant claims, while claims 10-13 recite specific acylated pyrimidines. Claims 16-23 recite the same additional active agents such as uridine phosphorylase inhibitors, cytidine deaminase inhibitors, and nucleoside transport inhibitors. Thus, the active method steps herein are seen to be same as the method in the patent. Therefore claims 1-23 of '914 anticipate the claimed invention.

The following rejections of record in the previous office action are maintained:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 and 8-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 4, and 8 of U.S. Patent No. 6743782. (of record in previous office action, herein referred to as '782) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 3, 4, and 8 of '782 claim subject matter which substantially overlaps with the claimed subject matter. These claims are directed to methods for delivering exogenous deoxyribonucleosides to any subject (e.g. an animal) by administering an acylated non-methylated pyrimidine. Column 19 lines 9-17 of the specification indicate that the subject described in the claims is interpreted to include a subject having damaged bone marrow from chemotherapeutic treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer these compounds to a subject suffering from toxicity due to administration of chemotherapeutic or antiviral pyrimidine nucleoside analogs. One of ordinary skill in the art would have found thins method to be obvious because it substantially overlaps with the methods claimed by claims 3, 4, and 8 of '782.

Response to Argument: Applicant's arguments, submitted December 21, 2007, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the aforementioned claims

of '782 are not directed toward methods for treating cancer. However, the instant claims are not directed to a method for treating cancer either but merely to a method of administering an acylated pyrimidine to an animal. The preamble to the claim, "for preventing or treating toxicity due to a pyrimidine nucleoside analog," is not seen to limit or define the scope of the instant claims as the claims broadly recite "administering to an animal". Thus, the claims do not limit patient population. Therefore the rejection is deemed proper and maintained.

Claims 1-5 and 8-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, and 5 of U.S. Patent No. 6103701. (of record in previous office action, herein referred to as '701) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4, and 5 of '701 claim subject matter which substantially overlaps with the instantly claimed subject matter. These claims are directed to methods for delivering exogenous deoxyribonucleosides to a subject (e.g. an animal) by administering an acylated non-methylated pyrimidine. Column 19 lines 48-56 of the specification indicate that the subject described in the claims is interpreted to include a subject having damaged bone marrow from chemotherapeutic treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer these compounds to a subject suffering from toxicity due to administration of chemotherapeutic or antiviral pyrimidine nucleoside analogs. One of

ordinary skill in the art would have found thins method to be obvious because it substantially overlaps with the methods claimed by claims 1, 4, and 5 of '701.

Response to Argument: Applicant's arguments, submitted December 21, 2007, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the aforementioned claims of '701 are not directed toward methods for treating cancer. However, the instant claims are not directed to a method for treating cancer either but merely to a method of administering an acylated pyrimidine to an animal. The preamble to the claim, "for preventing or treating toxicity due to a pyrimidine nucleoside analog," is not seen to limit or define the scope of the instant claims. Therefore the rejection is deemed proper and maintained.

Claims 1-5 and 8-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-12 and 22-25 of U.S. Patent No. 6306834. (of record in previous office action, herein referred to as '834) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-12 and 22-25 of '834 claim subject matter which substantially overlaps with the instantly claimed subject matter. These claims are directed to methods for delivering exogenous deoxyribonucleosides to a subject (e.g. an animal) by administering an acylated non-methylated pyrimidine. Column 19 lines 9-17 of the specification indicate that the subject described in the claims is interpreted to include

within its scope a subject having damaged bone marrow from chemotherapeutic treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer these compounds to a subject suffering from toxicity due to administration of chemotherapeutic or antiviral pyrimidine nucleoside analogs. One of ordinary skill in the art would have found thins method to be obvious because it substantially overlaps with the methods claimed by claims 9-12 and 22-25 of '834.

Response to Argument: Applicant's arguments, submitted December 21, 2007, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the aforementioned claims of '834 are not directed toward methods for treating cancer. However, the instant claims are not directed to a method for treating cancer either but merely to a method of administering an acylated pyrimidine to an animal. The preamble to the claim, "for preventing or treating toxicity due to a pyrimidine nucleoside analog," is not seen to limit or define the scope of the instant claims. Therefore the rejection is deemed proper and maintained.

Claims 1-5 and 8-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6348451. (of record in previous office action, herein referred to as '451) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11 of '451 claim subject matter which substantially overlaps with the instantly claimed

subject matter. These claims are directed to methods for promoting wound healing in an animal by administering an acylated non-methylated pyrimidine. (cytosine) Column 19 lines 9-17 of the specification indicate that the subject described in the claims is interpreted to include within its scope a subject having damaged bone marrow from chemotherapeutic treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer these compounds to a subject suffering from toxicity due to administration of chemotherapeutic or antiviral pyrimidine nucleoside analogs. One of ordinary skill in the art would have found this method to be obvious because it substantially overlaps with the methods claimed by claims 1-11 of '451.

Response to Argument: Applicant's arguments, submitted December 21, 2007, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the aforementioned claims of '451 are not directed toward methods for treating cancer. However, the instant claims are not directed to a method for treating cancer either but merely to a method of administering an acylated pyrimidine to an animal. The preamble to the claim, "for preventing or treating toxicity due to a pyrimidine nucleoside analog," is not seen to limit or define the scope of the instant claims. Therefore the rejection is deemed proper and maintained.

Claims 1-5, 8-11, and 14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S.

Patent No. 6329350. (of record in previous office action, herein referred to as '350) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-7 of '350 claim subject matter which substantially overlaps with the instantly claimed subject matter. These claims are directed to methods for treating cancer by administering to an animal an acylated non-methylated pyrimidine. (cytosine) Claim 3 specifically identifies the acylated pyrimidine as triacetyluridine. Column 4 lines 36-42 of the specification indicate that the subject described in the claims is interpreted to include within its scope a subject having damaged bone marrow from chemotherapeutic treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer these compounds to a subject suffering from toxicity due to administration of chemotherapeutic or antiviral pyrimidine nucleoside analogs. One of ordinary skill in the art would have found this method to be obvious because it substantially overlaps with the methods claimed by claims 1-7 of '350.

Response to Argument: Applicant's arguments, submitted December 21, 2007, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the aforementioned claims of '350 are not directed toward methods for treating cancer. However, the instant claims are not directed to a method for treating cancer either but merely to a method of administering an acylated pyrimidine to an animal. The preamble to the claim, "for preventing or treating toxicity due to a pyrimidine nucleoside analog," is not seen to limit

or define the scope of the instant claims. Therefore the rejection is deemed proper and maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
3/25/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623